REMARKS

Upon entry of the amendment, claims 12-13, 16-21, 25-27, 32-37, 41-52, and 54-77 are pending. Claims 12, 13, 25, 41, 44, 46-49, 51, 55, 62, and 65-67 have been amended. Claims 14, 15, 22-24, 28-31, 38-40, and 53 are canceled. Although the Examiner states on page 2 of the instant Office Action that only claims 12-22, 25-27, 30-38, and 41-49 were pending as of the mailing date of the Office Action. However, Applicants submit that claims 50-77 were also pending. It appears from the Office Action that the Examiner considered claims 50-77 regardless of page 2 of the Office Action.

Rejections Under 35 U.S.C. §102(e) over U.S. Patent No. 6,025,127 to Sidransky

The Examiner rejected claims 12-14, 16-22, 25-26, 30-38, and 42-45 under 35 U.S.C. §102(e) as being anticipated by U.S. Patent No. 6,025,127 (Sidransky). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Anticipation under 35 U.S.C. §102 requires that all of the elements and limitations of the claims at issue be found within a single prior art reference. *Carella v. Starlight Archery and Pro Line Co.*, 804 F.2d 135, 231 U.S.P.Q. 644 (Fed. Cir. 1986).

Sidransky does not teach all the elements and limitations of Applicants' claims. Sidransky does not identically disclose replacement nucleic acids that have at least one altered wobble base in at least one codon to avoid targeting and binding of the replacement nucleic acid by a suppression effector. Sidransky does not provide any guidance as to the nature of such a replacement gene or how a replacement gene would avoid being suppressed by a suppression effector (*e.g.*, such as an antisense nucleic acid or ribozyme).

Applicants submit below the sentences in Sidransky that contain mention of replacement genes or replacement therapy. Contrary to the Examiner's assertion, changes in wobble bases, as

required by the claims, are not taught or suggested. In fact, the words "degeneracy" or "wobble" are not mentioned at all in Sidransky.

> Methods for treatment of cell proliferative diseases utilizing ribozymes or antisense oligonucleotides specific for the target mutant nucleic acids and/or **replacement wild type genes** are also disclosed. (Sidransky, abstract, second sentence, emphasis added).

> However, when the mutation is dominant, as in Type I mutations, and in cases wherein either both alleles are deleted or one is deleted and the other is mutant, as in certain Type III mutations, antisense therapy is preferably accompanied by replacement therapy. In **replacement therapy a wild type gene** is introduced into the target cells identified as having a mutant tumor suppressor gene or protooncogene which results in production of the wild type protein necessary to forestall development of the neoplasia associated with the identified mutant gene(s). (Sidransky, column 13, lines 47-57, emphasis added).

> Thus, in cases where ribozyme and/or antisense therapy is accompanied by gene replacement therapy, the chances are increased that the cell population containing the mutant gene for which the ribozyme or antisense oligonucleotide is specific will no longer contribute to development of neoplasia in the subject being treated. (Sidransky, column 13, lines 61-67).

> Such therapy would achieve its effect by introduction of the specific antisense polynucleotide and/or **replacement wild type gene** into cells identified by the methods of this invention as having the proliferative disorder caused by mutated genes. Whether the cell will require replacement of the wild type gene encoding the tumor suppressor gene or proto-oncogene as well as antisense therapy to prevent replication of the mutant gene must be determined on a case by case basis and will depend upon whether the mutation has a dominant effect, ie., whether both alleles of the wild type gene have been destroyed so that total absence of the gene has a cell proliferative effect. (Sidransky, column 14, line 65 to column 15, line 10, emphasis added).

> Delivery of antisense proto-oncogene or tumor suppressor polynucleotides specific for mutated genes as well as of **replacement wild type genes** can be achieved using a recombinant expression vector such as a chimeric virus or a colloidal dispersion system. (Sidransky, column 15, lines 11-15, emphasis added)

> A separate vector can be utilized for targeted delivery of a replacement gene to the cell(s), if needed, or the antisense oligonucleotide and the replacement gene can optionally be delivered via the same vector since the antisense oligonucleotide is specific only for the mutant target gene. (Sidransky, column 15, lines 43-48).

None of the above excerpts from Sidransky mention a replacement nucleic acid that varies from the mutant nucleic acid (i.e., suppression effector target) by having one or more degenerate/wobble sites that are altered so that the replacement nucleic acid is not inhibited by the suppression effector. This was not contemplated by Sidransky. Applicants respectfully submit that the Examiner's assumption that Sidransky "contemplates the design of suppression effector that targets a mutant allele that differs from a replacement nucleic acid by at least one degenerate/wobble site" is not supported by Sidransky's specification.

Sidransky reports methods for detecting a number of p53 mutations in tissue samples and suppression by antisense nucleic acid or ribozyme molecules that target p53 mutations. Although Sidransky makes a general suggestion that suppression of certain mutant p53 genes may be accompanied by replacement therapy, Sidransky does not provide any guidance as to the nature of such a replacement gene or how a replacement gene would avoid being suppressed by an antisense nucleic acid, ribozyme, or other suppression effector. Even if Sidransky discloses p53 mutations detected in tumor tissue (Table 2) which comprise a single nucleotide change in a wobble position of a codon compared to a wild-type p53 sequence, Sidransky **does not** disclose, or provide a motivation to create, a **replacement nucleic acid** that has at least one altered wobble base.

Applicants further submit that Sidransky only discloses replacement wild type genes (see bolded text above) and does **not** provide any further description of his replacement gene. Thus Sidransky only contemplates a replacement gene that is not recognized by Sidransky's suppressor because the replacement gene does not contain the mutant sequence recognized by the suppressor. On the contrary, Applicants' invention does not require a wild type replacement gene, but rather can use a mutant (i.e., engineered to be altered at any number of

wobble/degenerate bases) replacement nucleic acid that encodes a wild type or non-disease-causing protein.

Sidransky therefore does not identically disclose each and every element of Applicants' claims and therefore is not a proper reference under 35 U.S.C. §102(e). Applicants respectfully request that the rejection be reconsidered and withdrawn.

Rejections Under 35 U.S.C. §102(b) over Robinson-Benion *et al.* (1994) Leukemia 8:s152-s155

The Examiner rejected claims 12, 14, 21, 26-27, 33, 42-44, 51, 53, 55, 59, 61, 63-64, 70-71, 73, and 75-77 under 35 U.S.C. §102(b) as being anticipated by Robinson-Benion *et al.* (1994) Leukemia 8:s152-s155 (Robinson-Benion). Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Robinson-Benion does not identically disclose each and every element of Applicants' invention. First, Robinson-Benion does not disclose targeting a mutant allele but only discloses targeting a wild-type allele. Second, Robinson-Benion does not disclose suppression effectors that bind to a protein coding region of a mature RNA (*e.g.*, independent claims 12, 44, and 51). On the contrary, Robinson-Benion discloses only an 84 bp anti-fos antisense RNA that is complementary to the 5' **untranslated** region of mouse c-fos gene (see Robinson-Benion, page s153, column 1, first paragraph entitled "Anti-fos RNA inhibits endogenous c-fos but not antisense resistant mutant fos gene", lines 1-6). Applicants submit that the 5' untranslated region is not part of the coding region of an RNA (*e.g.*, it does not code for protein). Consequently, the antisense-resistant mutant fos gene (*i.e.*, Robinson-Benion replacement gene) lacks the 84 bp of 5' untranslated region that the antisense targets (see Robinson-Benion, page s152, column 2, second paragraph entitled "Plasmid Construction", lines 1-5). Since the Robinson-Benion antisense was directed at untranslated region, there would be no corresponding "wobble" bases (which are only found to protein coding sequence) to alter in their replacement gene. The only alteration described in Robinson-Benion's replacement gene is that it lacks the 84 bases in the 5' untranslated region of the c-fos gene. Given that Robinson-Benion does not identically disclose

each and every element of Applicants' claims, Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections Under 35 U.S.C. §112, first paragraph

The Examiner rejected claims 12, 25, 41-44, 51, 62-64, 70-71, 73, and 75-77 under 35 U.S.C. §112, first paragraph, contending that they read on antibodies and peptides. Not in acquiescence of the rejection but in order to expedite allowance of the claims, Applicants have amended, without prejudice to pursue claims of a greater or lesser scope in a continuation or divisional application, independent claims 12, 44, and 51 to recite nucleic acids or peptide nucleic acids. Applicants submit that the rejection is thereby rendered moot and therefore respectfully request reconsideration and withdrawal of the rejection.

The Examiner also rejected claims 46-49 and 65-67 under 35 U.S.C. §112, first paragraph, contending that they lacked enablement because the ribozyme sequences claimed are directed to DNA sequences. Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Applicants submit that the Specification provides detailed enablement for how to make and use the ribozymes of the invention and that a skilled artisan would not require undue experimentation to practice Applicants' invention. Nevertheless, not in acquiescence of the rejection but in order to expedite allowance of the claims, Applicants have amended the claims to clarify that the sequences provided in the claims "encode" ribozymes by insertion of the language "a nucleotide sequence encoded by". Applicants submit that the rejection is rendered moot and respectfully request reconsideration and withdrawal of the rejection.

Double Patenting

The Examiner rejected claims 30, 32-37, 41-45, 52, 60-64, and 68-77 under the judicially created doctrine of obviousness-type double patenting over claims 77-140 of co-pending U.S. Application Serial No. 09/043,506. Applicants traverse the rejection to the extent it is maintained over the claims as amended.

Applicants submit that the instant claims are patentably distinct from the claims of allowed U.S. Patent Application Serial No. 09/043,506 ('506). The claims of '506 require a suppression effector that targets to an untranslated region. The claims of the instant application require a suppression effector that targets a coding region and also requires a replacement nucleic acid that has altered wobble bases. Although both applications describe suppression effectors and replacement nucleic acids, their targets are different and, as a consequence, their replacement nucleic acid are different.

The '506 application contains no disclosure that would render obvious the instant claims. Since the target in '506 is an untranslated region, it would not have been obvious to have a replacement nucleic acid that has altered wobble bases, in fact because this would be inoperative. There would therefore be no motivation to have such an altered replacement nucleic acid. There would also be no reason to change targets to target a coding sequence, given that '506 does not provide a disclosure of how to make a functional replacement nucleic acid for a coding sequence. Applicants submit that the Examiner is using hindsight to obtain a finding of obviousness, which is improper.

Conversely, the instant application requires the use of a replacement nucleic acid that has altered wobble bases. It therefore would not have been obvious to target an untranslated region as in '506, because the instant replacement nucleic acid would not work with such a target, which does not contain wobble bases.

Regarding the issue of co-ownership, there is no reason to believe that '506 and the instant application should be co-owned, given that they claim different targets and the different replacement nucleic acids. Applicants therefore submit that the filing of a terminal disclaimer is not necessary.

Applicants respectfully request that the rejection be reconsidered and withdrawn.

REQUEST FOR TELEPHONIC INTERVIEW

The undersigned respectfully requests a telephonic interview with Examiner Epps Ford *prior* to issuance of a further Office Action in the instant application. The undersigned believes

that an interview with Examiner Epps Ford may be sufficient to resolve any issues remaining in the case. The Examiner is invited to telephone Diana Steel at 617-310-8168 to arrange a convenient time for the interview.

CONCLUSION

Applicants respectfully urge that all claims are in condition for allowance and request prompt and favorable action on the instant application. If the Examiner believes that a telephonic interview with the undersigned would expedite prosecution of this application, the Examiner is cordially invited to call the undersigned at (617) 310-8168.

Respectfully submitted,

Date: March 4, 2004
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